

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

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Applicant's or agent's file reference PV/326/PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/CZ 03/00058	International filing date (day/month/year) 21.10.2003	Priority date (day/month/year) 24.10.2002
International Patent Classification (IPC) or both national classification and IPC C07C269/00		
Applicant ZENTIVA, A.S. et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 4. sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 5 sheets.

- This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 09.04.2004	Date of completion of this report 05.11.2004
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bedel, C Telephone No. +49 89 2399-2506



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/CZ 03/00058**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1, 2, 6-14 as originally filed
3-5 received on 17.04.2004 with letter of 09.04.2004

Claims, Numbers

1-6 received on 17.04.2004 with letter of 09.04.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form;
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/CZ 03/00058**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-6
	No: Claims	
Inventive step (IS)	Yes: Claims	1-6
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-6
	No: Claims	

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CZ 03/00058

The amendments filed with letter dated 9-04-04 are in conformity with the requirements of Article 34 PCT. New claim 1 is supported by a combination of original claims 1 and 3 with a passage of page 5, lines 4-8.

The application now concerns a process in 4 steps for making an optically active rivastigmine of formula II.

- D1: CHEN CHUNG-PIN: TETRAHEDRON LETTERS, vol. 32, no. 49, 1991, pages 7175-7178, XP009025296
- D2: US-A-5 602 176 (ENZ ALBERT) 11 February 1997 (1997-02-11)
- D3: CISZEWSKA GRAZYNA: J.LABELLED COMPD.RADIOPHARM., vol. 39, no. 8, 1997, pages 651-668, XP002269029
- D4: EP-A-0 193 926 (YISSUM RES DEV CO) 10 September 1986 (1986-09-10)

D1 discloses the optically active the S-m-hydroxyphenylethyldimethylamine (key intermediate in the present process).

D2 discloses the resolution of racemic rivastigmine with a tartrate salt.

D3 discloses a process for making optically active rivastigmine by asymmetric reduction to obtain the methoxy intermediate.

D4 discloses the formation of rivastigmine by reaction of carbamoyl chloride with the hydroxy intermediate (last step in present process).

D3 which is the closest prior art differs from the presently claimed process by the fact that the asymmetric carbon is introduced through an asymmetric reduction to get the S-m-methoxyphenylethyldimethylamine, which is demethylated to obtain the S-m-hydroxyphenylethyldimethylamine (see p.655, reaction scheme cpd15 -->cpd 19), while the presently claimed process makes a resolution of the racemic m-hydroxyphenylethyldimethylamine intermediate.

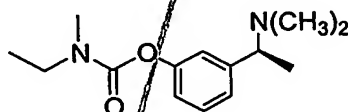
No other document discloses nor suggest the resolution of this intermediate to get the optically active rivastigmine.

The skilled person would have no indication in the prior art to use such a solution in order to develop an alternative process for the preparation of optically active rivastigmine.

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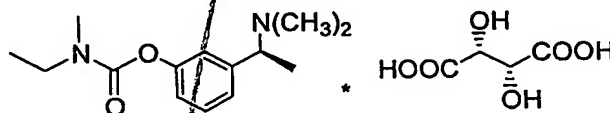
CLAIMS

1. A method of production of (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate, i.e. rivastigmine of formula II



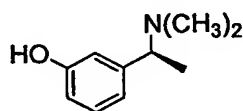
II

or of its hydrogentartrate of formula I



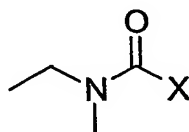
I

characterized in that the compound of formula III



III

optionally its alkali salt, is reacted with a compound of formula VII

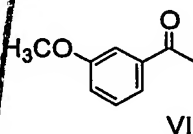


VII

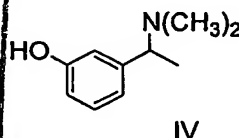
wherein X is a leaving group, resulting in the compound of formula II, which is then optionally converted, by reacting with tartaric acid, into the compound of formula I.

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ART 34 AMDT

2. The method according to claim 1 *characterized in that* the compound of formula III is converted, by reacting with a strong base, into an alkaline salt, which is subsequently reacted with the compound of formula VII.
3. The method according to claim 1 or 2 *characterized in that* the compound of formula III is obtained by transforming methoxyacetophenone of formula VI



into racemic amine of formula IV



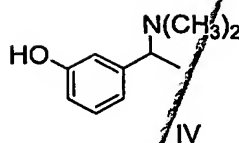
which is further resolved by reacting with an optically active acid, whereafter the desired respective diastereoisomer is crystallized and finally converted into the compound of formula III.

4. The optically active compound having absolute configuration (S) of formula III



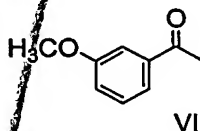
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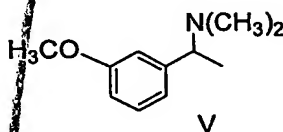


by reacting with an optically active acid, crystallizing the respective diastereoisomer and subsequently isolating the optically active phenol III.

The racemic phenol of formula IV can be obtained by reductive amination of methoxyacetophenone of formula VI



and subsequent O-dealkylation of the compound of formula V



The reductive amination is carried out by means of dimethylamine or its hydrochloride and a reduction agent, usually a hydride such as sodium borohydride.

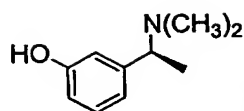
The O-dealkylation agents can be selected from among strong acids, such as for example hydrobromic acid, or from among boron halides, such as boron bromide.

As is demonstrated in the examples of especially preferred embodiments, the present method makes it possible for obtaining the product of formula I in an especially high optical purity. A reproduction of the method known so far, even with recrystallization, has not resulted in obtaining such high optical purity.

It further results from comparison that use of the optically active compound of formula III results in lowering of the consumption of the expensive and carcinogenic N-ethyl-N-methylcarbamoylchloride (corresponding to general formula VII for X = Cl) by 2/3.

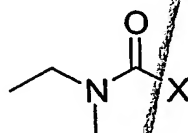
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III

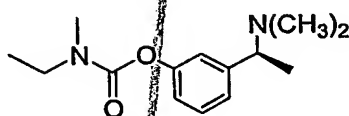
which is, optionally in the form of its alkali salt, reacted with a carbamoylhalide of formula VII



VII

wherein X is a leaving group.

The resulting compound of formula II



II

is converted, by reacting with tartaric acid, into the respective salt of formula I.

Advantageously, the phenol of formula III is converted with a strong base in an inert solvent into the phenolate and it is reacted with the carbamoylhalide of formula VII.

As the strong base, hydrides of alkali metals, such as sodium hydride, or alkyl lithium compounds such as butyl lithium, can be used. The inert solvent is preferably chosen from the group of dialkyl ethers such as tetrahydrofuran or 1,2-dimethoxyethan.

The respective optically active phenol of formula III has not been described yet and it can be obtained by resolving the racemic phenol of formula IV

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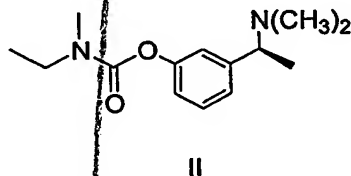
formula VII (mostly specifically N-ethyl-N-methylcarbamoyl chloride) in an about 300% excess is another drawback

Resolution in an earlier stage of the synthesis appears, at first sight, as desirable, but far from being feasible. There remains the question whether it is possible to obtain enantiomerically pure intermediates and, especially, whether these products can be used for further synthesis without being subject to racemization. The necessity of recrystallization would cast doubts on advantageousness of such procedure.

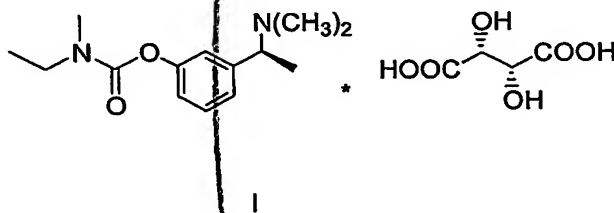
It has now turned out that optically resolving the intermediate products (i.e. performing the operation in an earlier stage of production) and performing the final step with an optically active substance, permits to obtain a very good yield of (S)-rivastigmine with retaining high analytic purity.

Disclosure of Invention

The present invention consists in a method of production of (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate (rivastigmine) of formula II



or of its hydrogentartrate of formula I



starting from the optically active phenol of formula III

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